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| (21) International Application Number: PCT/US96/00729 (22) International Filing Date: 19 January 1996 (19.01.96) (30) Priority Data: 08/374,424 19 January 1995 (19.01.95) US (71) Applicant (for all designated States except US): CYGNUS, INC. [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): AUDETT, Jay [US/US]; Apartment 90, 1200 Dale Avenue, Mountain View, CA 94040 (US). BESTE, Russell, D. [US/US]; 950 High School Way #3219, Mountain View, CA 94041 (US). FARINAS, Kathleen [US/US]; 2207 16th Avenue, San Francisco, CA 94116 (US). PUTNAM, Wendy [US/US]; 2015 Parrott Drive #2, San Mateo, CA 94402 (US). (74) Agents: KONSKI, Antoinette, F. et al.; Morrison & Foerster, L.L.P., 755 Page Mill Road, Palo Alto, CA 94304-1018 (US). | | (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: POLYISOBUTYLENE ADHESIVES CONTAINING HIGH T _g TACKIFIER FOR TRANSDERMAL DEVICES (57) Abstract Polyisobutylene adhesive compositions in the form of the basal layer of a laminated composite transdermal or transmucosal patch and which contain sufficient nicotine to plasticize the polyisobutylene adhesive and a sufficient amount of a polyisobutylene compatible, high T _g , low molecular weight tackifier to increase the tackiness of the layer. | | |

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POLYISOBUTYLENE ADHESIVES CONTAINING HIGH T_g TACKIFIER
FOR TRANSDERMAL DEVICES

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Description

Technical Field

This invention is in the field of transdermal or transmucosal drug delivery patches. More particularly it concerns polyisobutylene (PIB) adhesive compositions that are used to affix such patches to skin or mucosa.

Background

In many transdermal patch designs the basal layer is composed of a pressure sensitive adhesive. One type of pressure sensitive adhesive that is commonly used is PIB adhesive. PIB adhesives comprise a mixture of high molecular weight (HMW) PIB and low molecular weight (LMW) PIB. They often include plasticizers/tackifiers such as mineral oil or polybutene to alter the permeability of the adhesive to the drug or the tackiness of the adhesive.

Maintaining the adhesive properties of the adhesive in the presence of the drug or permeation enhancer is often difficult. With non-PIB adhesives (e.g. silicones, acrylates) many drugs/enhancers act as solvents and cause the mechanical or adhesive properties of the adhesive to degrade. PCT/US 91/02516 describes this problem and teaches that oily, non-polar drugs such as nicotine and other amines that solvate non-PIB adhesives can be delivered from PIB adhesives that are substantially free of plasticizers and tackifiers.

Applicants, however, found that PIB adhesives that are highly plasticized by such drugs have reduced tack. Applicants also found that the conventional tackifiers used with PIB, such as polybutene, were relatively ineffective in improving the tackiness of such PIB-drug formulations. The conventional tackifiers have low ($\ll 20^{\circ}\text{C}$) glass transition temperatures (T_g).

Surprisingly, however, applicant found that certain high T_g tackifiers effectively improved the tackiness of such formulations.

High T_g aliphatic resin-based tackifiers are commercially available, e.g., from Exxon Chemical under the trademark ESCOREZ. These tackifiers are known to tackify a variety of adhesives, including polyisobutylene. Applicants are not aware of any prior use of ESCOREZ® resins to tackify polyisobutylene adhesives used in transdermal patches that deliver drugs or enhancers that plasticize polyisobutylene adhesives.

Disclosure of the Invention

One aspect of the invention is a polyisobutylene adhesive composition in the form of a layer of a laminated composite transdermal or transmucosal patch for administering a drug and optionally a permeation enhancer which drug and/or enhancer are capable of plasticizing the polyisobutylene adhesive, said composition having:

- (a) a sufficient amount of said drug and/or enhancer dissolved therein to plasticize the adhesive; and
- (b) a sufficient amount of a polyisobutylene compatible, low molecular weight, high T_g tackifier to increase the tackiness of the adhesive.

Another aspect of the invention is an improvement in a laminated composite transdermal patch for administering a drug and optionally a permeation enhancer which drug and/or enhancer are capable of plasticizing polyisobutylene adhesives. The patch includes a polyisobutylene adhesive basal layer that contains a sufficient amount of the drug and/or enhancer to plasticize the adhesive. The improvement is to add to the adhesive a sufficient amount of a polyisobutylene-compatible, low molecular weight high Tg tackifier to increase the tackiness of the layer.

Modes For Carrying Out The Invention

The polyisobutylene adhesive compositions of this invention are in the form of a layer of a laminated composite transdermal or transmucosal drug delivery patch. The layer either constitutes the principal drug containing element of the patch or is at least partly "in-line" with that element. The term "in-line" means that the layer lies in the diffusional pathway through which the drug travels as it diffuses from the element to the skin or mucosa. The principal drug-containing element of the patch is often called the "drug reservoir" of the patch. Typically the layer will define the basal surface of the patch, i.e., the surface that directly contacts the skin or mucosa when the patch is worn.

When the layer constitutes the drug reservoir and defines the basal surface of the patch, the patch will also typically include a backing layer that overlies the adhesive layer. In addition such patches will typically have a release liner layer that underlies the adhesive layer prior to the time the patch is worn and which is removed from the patch prior to wearing. The composition and structure of backing layers and release liner layers are well known in the art and

do not require reiteration herein. The adhesive layer may also include other components such as non-woven fabric that are used in the manufacture of the patch.

When the layer does not constitute the drug
5 reservoir of the patch the patch will include a separate drug reservoir. The drug reservoir may be in the form of a matrix (solid or semi-solid layer) or a liquid reservoir formed between other layers of the patch. Such patches will also include a backing layer and release liner layer as described
10 above. They may also include other layers to provide structural support or to control the release rate of drug from the patch. Layers that control the release rate of drug are sometimes referred to as "release rate controlling membranes" in the art.

15 The polyisobutylene of the adhesive composition is itself a mixture of HMW PIB and LMW PIB. Such mixtures are described in the art, e.g., PCT/US 91/02516. The molecular weight of the HMW PIB will usually be in the range of about 700,000 to 2,000,000 Da whereas that of the LMW PIB will
20 typically range between 35,000 to 60,000 Da. The molecular weights referred to herein are weight average molecular weight, \bar{M}_w . The weight ratio of HMW PIB to LMW PIB in the adhesive will usually range between 1:1 to 0.2:1. The polyisobutylene adhesives of this invention are not hot melt
25 adhesives.

The tackifiers that are useful in the PIB adhesive compositions of the invention may be characterized as being PIB compatible and having a high Tg (typically in the range of 20°C to 100°C, preferably 30°C to 80°C) and a low molecular
30 weight (typically less than 5,000, preferably between 300 and 3000). The term "PIB compatible" intends a tackifier that is soluble in PIB and does not adversely affect the processing,

adhesive, mechanical or rheological properties of PIB.

Preferred tackifiers are the aliphatic hydrocarbon resins made by copolymerizing lower (C_4 - C_8) diolefins with lower (C_4 - C_8) monoolefins or polymerizing and hydrogenating cycloolefins such tackifiers are available from, for example, Hercules, Arizona Chemicals and Exxon Chemical. Particularly preferred are the aliphatic hydrocarbon resins sold commercially by Exxon Chemical as ESCOREZ® 1310LC resin and the ESCOREZ® 5000 Series resins. These particularly preferred resins are respectively copolymers of piperylene and 2-methyl-2-butene, and a thermopolymerized, hydrogenated cyclopentadiene. The wt% of tackifier in the adhesive composition will usually be in the range of 20% to 70%, more usually 30% to 60%.

The drug and/or the optional skin permeation enhancer that is/are present in the PIB adhesive composition will plasticize or solvate the PIB adhesive. Such drugs/enhancers are typically oily and non-polar. Such drugs are exemplified by nicotine, benztropine, secovirine, arecoline, and nitroglycerine. Examples of such enhancers are fatty acid esters such as isopropyl mysistrate, methyl oleate, methyl laurate, propylene glycol monolaurate, and 2-hydroxy ethyl esters of oleic acid. The amount of drug/enhancer present is sufficient to plasticize the PIB adhesive. Plasticization can be measured by increase in the dynamic viscosity. The drug will usually constitute 3% to 30% by weight, more usually 10% to 20% by weight of the PIB adhesive composition. When present the enhancer will constitute 1% to 30% by weight of the composition.

In addition to the PIB adhesive, tackifier and drug (and optional enhancer), the PIB adhesive composition may contain sorptive fillers or stiffeners such as silica gel, dyes, pigments, and other conventional additives that do not

deleteriously affect the properties of the composition. When the drug in the formulation is nicotine, the formulation preferably contains 2.0% to 20% by weight of sorptive silica gel.

5 The PIB adhesive compositions of the invention may be formulated by conventional mixing and blending procedures used in the art. Similarly, the patches that include the compositions may be fabricated by convention art procedures. See, for example, U.S. 4,915,950.

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The following examples further illustrate the adhesive compositions of the invention and the transdermal patches in which they are used. These examples are not intended to limit the invention in any manner.

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Examples

Three different sets of prototype transdermal patches were made as follows.

20 Solutions of HMW PIB (Exxon Vistanex MML-100, M.W. 1,060,000-1,440,000) and LMW PIB (Exxon Vistanex LM-MS-LC, m.w. 42,600-46,100) in hexane were prepared. These solutions were added to silica gel (W.R. Grace Siloid 244FP) wet with hexane and either polybutene (Indopol H-1900, m.w. 2300), ESCOREZ® 1310LC resin, or ESCOREZ® 5300 resin tackifier and
25 blended until the combined mixture was homogeneous. The mixture of HMW PIB, LMW PIB, tackifier (hexane excluded) was in a weight ratio of 2:4:4. The weight ratio of that mixture to silica gel was 90:10.

30 Each blend was cast onto release liner film (Polyslik 2016, Release International) to a wet thickness of approximately 15 mils and dried. A nonwoven polyester film (Veratec Novonette) was laminated onto one segment of the

release liner-adhesive assembly and a polyester backing film (Courtauld 92 gauge) was laminated onto another segment of that assembly. The laminates were die-cut into 20 cm² pieces.

5 Nicotine was sprayed onto the 20 cm² nonwoven polyester assembly, the release liner was removed from the segment to which the backing layer had been laminated and the two assemblies were laminated together with the adhesive side of the backing layer assembly contacting the nonwoven
10 polyester side of the other assembly. The resulting laminated composite consisted of: the backing layer, a combined adhesive layer in which the nonwoven polyester is imbedded, and a release liner layer. The thickness of the combined adhesive layer was 13 mils and it contained a nicotine loading
15 of 2.9 mg/cm².

 Adhesion tests on each of the three types of prototype patches were made in quadruplicate. The release liner layer was removed from the prototypes and the patches were placed adhesive side down onto a polyethylene substrate.
20 Approximately 4.5 psi pressure was applied to the patches with a roller. One minute after applying the pressure the patches were peeled from the substrate using an Instron machine.

 The average force required to peel the patches
25 containing polybutene tackifier from the substrate was 386±31 g/in. In comparison the average forces required to remove the patches containing ESCOREZ® 1310LC resin and ESCOREZ® 5300 resin, respectively, were 808±81 g/in. and 761±101 g/in. These results evidence the unexpected superiority of the
30 invention formulations (containing ESCOREZ® resin) relative to a prior art formulation (containing polybutene).

Rheological tests were also carried out to determine the storage moduli of each of the three formulations. These tests were carried out using a Rheometrics RMS-800 rheometer to measure the dynamic mechanical properties in the linear viscoelastic regime in the frequency range 0.01-100 rad/sec at 25°C. The tests showed that at a frequency of 100 rad/sec, the adhesive formulations that contain ESCOREZ® resin had higher storage moduli than the adhesive formulation that contained polybutene. The higher moduli of the ESCOREZ® resin-containing adhesives indicate they are tougher than the polybutene-containing resin. The increased toughness provides increased adhesion.

All patents and publications cited heretofore are incorporated herein by reference in their entireties.

Modifications of the above-described modes for carrying out the invention that are obvious to persons of skill in the field of transdermal patch fabrication are intended to be within the scope of the following claims.

Claims

We claim:

- 5 1. A polyisobutylene adhesive composition in the form of a layer of a laminated composite transdermal patch for administering a drug and optionally a skin permeation enhancer, at least one of said drug and enhancer being capable of plasticizing the polyisobutylene adhesive, said composition having:
- 10 a) a sufficient amount of said drug and/or enhancer dissolved therein to plasticize the polyisobutylene adhesive; and
- b) a sufficient amount of a polyisobutylene compatible, high Tg, low molecular weight tackifier to
- 15 increase the tackiness of the adhesive.
2. The composition of claim 1 wherein the drug is nicotine.
- 20 3. The composition of claim 2 wherein the nicotine constitutes 3% to 30% by weight of the composition.
4. The composition of claim 2 wherein the Tg of the tackifier is in the range of 20°C to 100°C and the molecular weight of the tackifier is less than 5000.
- 25 5. The composition of claim 2 wherein the tackifier is an aliphatic resin-based tackifier.
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6. The composition of claim 2 wherein the tackifier is a copolymer of piperylene and 2-methyl-2-butene or a thermopolymerized, hydrogenated cyclopentadiene.

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7. The composition of claim 2 wherein the tackifier constitutes 20% to 70% by weight of the composition.

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8. The composition of claim 6 wherein the composition includes 2% to 20% by weight sorptive silica gel.

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9. In a transdermal drug delivery patch for administering a drug and optionally a skin permeation enhancer, at least one of said drug and enhancer being capable of plasticizing polyisobutylene adhesive, and having a polyisobutylene adhesive basal layer containing a plasticizing amount of said drug and/or enhancer, the improvement wherein said layer contains a sufficient amount of a polyisobutylene-compatible, high Tg, low molecular weight tackifier to increase the tackiness of the layer.

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10. The patch of claim 9 wherein the drug is nicotine.

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11. The patch of claim 10 wherein the nicotine constitutes 3% to 30% by weight of the layer.

12. The patch of claim 10 wherein the Tg of the tackifier is in the range of 20°C to 100°C and the molecular weight of the tackifier is less than 5000.

5 13. The patch of claim 10 wherein the tackifier is an aliphatic resin-based tackifier.

10 14. The patch of claim 10 wherein the tackifier is a copolymer of piperylene and 2-methyl-2-butene or a thermopolymerized, hydrogenated cyclopentadiene.

15 15. The patch of claim 10 wherein the tackifier constitutes 20% to 70% by weight of the layer.

16. The patch of claim 14 wherein the layer contains 2% to 20% by weight of sorptive silica gel.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/00729

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC 6 A61K

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | EP,A,0 374 980 (NITTO DENKO CORPORATION) 27 June 1990 | 1,9 |
| Y | see page 6; example 6 | 2-8, 10-16 |
| | --- | |
| X | EP,A,0 204 968 (BEIERSDORF AKTIENGESELLSCHAFT) 17 December 1986 see the whole document | 1,9 |
| | --- | |
| X | EP,A,0 169 364 (BEIERSDORF AKTIENGESELLSCHAFT) 29 January 1986 see page 15; example 4A | 1,9 |
| | --- | |
| X | EP,A,0 379 045 (NOVEN PHARMACEUTICALS, INC.) 25 July 1990 see page 15; example 11 see page 16; example 12 | 1,9 |
| | --- | |
| | -/-- | |

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International Application No
PCT/US 96/00729

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y | WO,A,91 16085 (ALZA CORPORATION) 31 October 1991 cited in the application see the whole document --- | 2-8, 10-16 |
| A | GB,A,2 140 019 (ALZA CORPORATION) 21 November 1984 see claim 1 --- | 8,16 |
| A | EP,A,0 384 267 (LTS LOHMANN THERAPIE-SYSTEME GMBH & CO.KG) 29 August 1990 see claims 10,12 ----- | 8,16 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 96/00729

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date | |
|---|---------------------|----------------------------|---------------------|----------|
| EP-A-374980 | 27-06-90 | JP-A- | 4099720 | 31-03-92 |
| | | JP-B- | 7025669 | 22-03-95 |
| | | CA-A- | 2006511 | 23-06-90 |
| | | DE-D- | 68910947 | 05-01-94 |
| | | DE-T- | 68910947 | 17-03-94 |
| | | ES-T- | 2045377 | 16-01-94 |
| ----- | | | | |
| EP-A-204968 | 17-12-86 | DE-A- | 3518707 | 27-11-86 |
| | | AU-B- | 589852 | 19-10-89 |
| | | AU-B- | 5745786 | 27-11-86 |
| | | CA-A- | 1267606 | 10-04-90 |
| | | JP-A- | 61271219 | 01-12-86 |
| | | KR-B- | 9406105 | 06-07-94 |
| | | US-A- | 4776850 | 11-10-88 |
| ----- | | | | |
| EP-A-169364 | 29-01-86 | DE-A- | 3423293 | 02-01-86 |
| | | DE-A- | 3423328 | 02-01-86 |
| | | AU-B- | 579794 | 08-12-88 |
| | | AU-B- | 4304685 | 02-01-86 |
| | | AU-B- | 571980 | 28-04-88 |
| | | AU-B- | 4387885 | 02-01-86 |
| | | CA-A- | 1255175 | 06-06-89 |
| | | DE-A- | 3564073 | 08-09-88 |
| | | EP-A,B | 0170821 | 12-02-86 |
| | | JP-A- | 61015832 | 23-01-86 |
| | | JP-A- | 61040215 | 26-02-86 |
| | | US-A- | 4711781 | 08-12-87 |
| | | AU-B- | 579970 | 15-12-88 |
| | | AU-B- | 4304785 | 02-01-86 |
| | | CA-A- | 1247528 | 27-12-88 |
| | | DE-A- | 3560985 | 23-12-87 |
| | | EP-A,B | 0170010 | 05-02-86 |
| | | JP-A- | 61015833 | 23-01-86 |
| | | US-A- | 4699792 | 13-10-87 |
| ----- | | | | |
| EP-A-379045 | 25-07-90 | US-A- | 4994267 | 19-02-91 |
| | | AT-T- | 122240 | 15-05-95 |
| | | AU-B- | 632534 | 07-01-93 |
| | | AU-B- | 5034990 | 13-08-90 |
| | | CA-A- | 2044132 | 12-07-90 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/00729

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP-A-379045 | | DE-D- 69019175 | 14-06-95 |
| | | DE-T- 69019175 | 18-01-96 |
| | | EP-A- 0453505 | 30-10-91 |
| | | EP-A- 0634179 | 18-01-95 |
| | | ES-T- 2071683 | 01-07-95 |
| | | JP-B- 7093939 | 11-10-95 |
| | | JP-T- 4502719 | 21-05-92 |
| | | NL-A- 9020159 | 02-01-91 |
| | | PT-B- 92830 | 29-12-95 |
| | | US-A- 5405486 | 11-04-95 |
| | | WO-A- 9007940 | 26-07-90 |
| | | US-A- 5032207 | 16-07-91 |
| | | US-A- 5300291 | 05-04-94 |
| | | US-A- 5474783 | 12-12-95 |
| WO-A-9116085 | 31-10-91 | US-A- 5508038 | 16-04-96 |
| | | AT-T- 134512 | 15-03-96 |
| | | AU-B- 630817 | 05-11-92 |
| | | AU-B- 7852191 | 11-11-91 |
| | | CA-A- 2040352 | 17-10-91 |
| | | DE-D- 69117505 | 04-04-96 |
| | | EP-A- 0525105 | 03-02-93 |
| GB-A-2140019 | 21-11-84 | ES-T- 2084161 | 01-05-96 |
| | | US-A- 4559222 | 17-12-85 |
| | | AU-B- 558304 | 22-01-87 |
| | | AU-B- 2717184 | 08-11-84 |
| | | BE-A- 899444 | 16-08-84 |
| | | CA-A- 1217139 | 27-01-87 |
| | | CH-A- 666190 | 15-07-88 |
| | | DE-A- 3416248 | 08-11-84 |
| | | FR-A,B 2545357 | 09-11-84 |
| | | JP-C- 1770097 | 30-06-93 |
| | | JP-B- 4060091 | 25-09-92 |
| | | JP-A- 59206307 | 22-11-84 |
| | | NL-A,B,C 8401262 | 03-12-84 |
| | | SE-B- 463012 | 01-10-90 |
| | | SE-A- 8402389 | 05-11-84 |
| EP-A-384267 | 29-08-90 | DE-A- 3905051 | 30-08-90 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/00729

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP-A-384267 | | ES-T- 2058627 | 01-11-94 |
| | | JP-A- 2258717 | 19-10-90 |
| | | US-A- 5215751 | 01-06-93 |
| ----- | | | |